REMARKS

Claims 19 and 34 are pending in the present application. Claims 19 and 34 have been amended herein, and new claims 60 to 74 have been added. Upon entry of the amendment, claims 19, 34, and 60 to 74 will be under examination.

Support for the amendments and new claims

Claim 19 has been amended to move the "under suitable conditions" clause to the end of step (a) for increased clarity.

Claims 19 and 34 have been amended to recite that the effective agent alters the associate of CAP-1 with either CD40 or a polypeptide that contains a TRAF domain. Support for this amendment can be found throughout the specification, for example, at page 20, lines 22-25 and page 21, lines 1-5, and in claims 19 and 34 as originally filed.

New independent claim 63 is directed to a method of identifying an effective agent that alters association of CAP-1 with CD40. New independent claim 67 is directed to a method of identifying an effective agent that alters association of CAP-1 with CD40 in a test sample. New claims 63 and 67 are supported throughout the specification, for example, at page 20, lines 22-25, and by claims 19 and 34, respectively, as originally filed.

New independent claim 71 is directed to a method of identifying an effective agent that alters homodimerization of CAP-1. New claim 71 is supported throughout the specification, for example, at page 13, lines 24-26, page 49, lines 20-21, and by claim 19 as originally filed.

New claims 60, 65, 68 and 72 depend from claims 19, 63, 67, and 71, respectively, and recite a CAP-1 comprising amino acids 384 to 540 of SEQ ID NO:2, which corresponds to the TRAF domain of human CAP-1. Support for new claims 60, 65, 68 and 72 can be found throughout the specification, for example, at page 55, lines 18-23.

New claims 61, 64, 69 and 73 depend from claims 19, 63, 68, and 72, respectively, and recite a CAP-1 comprising amino acids 53 to 91 of SEQ ID NO:2, which corresponds to a RING finger motif of human CAP-1. Support for new claims 61, 64, 69 and 73 can be found throughout the specification, for example, at page 54, lines 24-26.

New claims 62, 66, 70 and 74 depend from claims 19, 63, 67, and 71, respectively, and recite a CAP-1 comprising amino acid sequence SEQ ID NO:2, which corresponds to full length human CAP-1. Support for new claims 62, 66, 70 and 74 can be found throughout the specification, for example, at page 18, lines 19-23.

As set forth above, the amendments and new claims are supported by the specification and do not add new matter. Accordingly, Applicants respectfully request that the Examiner enter the amendments and new claims.

Rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph

Claims 19 and 34 stand rejected under 35 U.S.C. § 101 as allegedly not supported by a substantial utility, a well established utility or a credible utility. Claims 19 and 34 also stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that since the claimed invention lacks a well established utility, one skilled in the art would not know how to use the claimed invention. In particular, the Office Action alleges that the specification lacks teaching of (a) whether binding of CAP-1 to CD40 results in any functional effect on the activity of CD40, and (b) the involvement of CAP-1 or an effective agent in the etiology or treatment of any specific disease. Applicants respectfully traverse the rejections for the reasons that follow.

Applicants submit that the specification teaches that an effective agent identified by practicing the claimed methods can be used to modulate association of CAP-1 with a second molecule for multiple *in vitro* and therapeutic purposes. In this regard, because CAP-1 can associate with various distinct polypeptides, including for example CD40 and TRAF domain containing polypeptides, an effective agent can be used for modulating various cellular functions, depending on the second

molecule selected. An exemplary effective agent described in the specification alters association of CAP-1 with CD40 (page 22, lines 8-13). The specification teaches that association of CAP-1 with CD40 can be used to manipulate signal transduction pathways controlled by CD40, for example, by blocking the Ig class-switching signal that results due to the binding of CD40L of a T_H cell with CD40 of a B cell (page 23, lines 1-3). Support for the premise that altering association of CAP-1 with CD40 can modulate Ig class-switching is provided, for example, by the teaching in the specification that CD40 function in B cells has been extensively studied and that this protein is believed to play an important role in regulation of Ig class-switching and other B cell functions (page 6, lines 15-28). The specification further describes that CAP-1 and CD40 can associate sufficiently specifically such that the bound complex can form *in vivo* in a cell (page 10, lines 23-26). Based on these teachings in the specification, Applicants submit that one skilled in the art would recognize that complex formation between a regulatory protein, such as CD40, and a CD40 binding protein, such as CAP-1, would be capable of altering a CD40 function such as Ig class-switching. Applicants have thus asserted at least one specific, substantial and credible utility for the effective agent identified using the claimed methods.

Without conceding that any burden has shifted to the Applicants to support an asserted utility with evidence of its credibility, Applicants submit herewith as Exhibit 1 a publication authored by co-inventor Dr. John C. Reed

(Leo et al., *Eur. J. Immunol.* 29:3908-3913 (1999)). The publication corroborates the teachings in the specification that association of CAP-1 with CD40 can modulate Ig class-switching. As is described in Leo et al., CD40 mediates activation of Ig-Cγ1- and Ig-Cε germ line promoters, which are involved in Ig gene expression and control of class switch recombination. The authors demonstrated that mutation of the CAP-1 (TRAF3) binding motif within the cytoplasmic tail of CD40 results in significant decreases in CD40-mediated Ig Cγ1- and Cε promoter activation, stating that:

> The CD40(Q263A) mutant which exhibits selective impairment in TRAF3 binding, for example, displayed only approximately 25 + 10% and 30 + 10% (n=3) the activity of WT CD40 at inducing the Cγ1- and Cε promoters, respectively ($\rho<0.01$; $\rho=0.04$), providing indirect evidence of a requirement for TRAF3 for optimal CD40-mediated Cγ1- and Cε promoter transcription. (page 3909, first column, second paragraph)

Further evidence of the importance of CAP-1 (TRAF3) in CD40-mediated activation of the Cγ1- and Cε promoters was provided in experiments employing a mutant TRAF3 having a deletion of the N-terminal RING domain (ΔN-TRAF3). The ΔN-TRAF3 mutant, which interferes with endogeneous TRAF3 function in a dominant negative manner, when co-expressed with CD40,

"almost completely abolished CD40-mediated activation of the Cγ1- and Cε promoters (page 3910, last paragraph)."

Therefore, regarding whether binding of CAP-1 to CD40 results in any functional effect on the activity of CD40, teaching in the specification that association of CAP-1 with CD40 can modulate the known function of CD40 in Ig class-switching is corroborated by the descriptions in Leo et al. of reduced CD40 function in the absence of CAP-1 association. Regarding the involvement of CAP-1 or an effective agent in the etiology or treatment of any specific diseases, Applicants submit that the specification teaches that an effective agent that alters association of CAP-1 with CD40 can be used to block the CD40-mediated Ig class-switching signal and thereby reduce the level of IgE production by an individual in order to treat atopic diseases mediated by IgE class immunoglobulin (page 23, lines 1-6). Leo et al. presents data supporting that association of CAP-1 with CD40 indeed alters CD40 function in regulating promoters that control class switch recombination and Ig gene expression and thus corroborates that altering association of CAP-1 with CD40 is a valid approach for modulating CD40-mediated Ig class-switching for therapeutic purposes.

To corroborate that CAP-1 is the same as TRAF3, applicants submit herewith as Exhibit 2 a definition of CAP-1 from the COPE Cytokines Online Pathfinder Encyclopaedia. The COPE definition of CAP-1 indicates that this molecule has been renamed TRAF-3.

The Office Action asserts the specification lacks description of methods for establishing effective doses for the identified effective agent. Applicants point out that the claims under examination are directed to methods for identifying an effective agent that alters the association of CAP-1 with a second polypeptide, and that the specification teaches a utility for an identified effective agent, which is corroborated by Leo et al. Although Applicants consider establishment of dosage irrelevant to the stated specific, substantial and credible utility of the claimed methods, Applicants respectfully submit that the specification provides sufficient guidance to allow one skilled in the art to determine an effective dose of an identified agent. In this regard, the specification teaches that factors to be considered when determining an effective dose in a subject include the age and general health of the subject, route of administration, number of treatments to be administered, and the chemical form of the agent (page 37, lines 18-24). With this guidance and given that procedures for determining appropriate dosages of compounds for administration were well known in the art at the time of filing the present application, those skilled in the art would have been able to administer an effective agent identified using a method of the invention without undue experimentation.

In view of the above remarks and accompanying Leo et al. publication, it is submitted that the claimed invention satisfies the requirements for utility and, therefore,

it is respectfully requested that the rejections under 35 U.S.C. § 101 and § 112, first paragraph, be removed.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, written description

The objection to the specification and corresponding rejection of claims 19 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description in the specification, are respectfully traversed. Applicants respectfully submit that the specification provides sufficient description to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

The Office Action acknowledges that methods of identifying an effective agent that alters the association of CAP-1 with CD40, CAP-1, TRAF-1 or TRAF-2 are supported by written description in the specification. However, it is alleged that the specification lacks enablement for practice of the claimed methods with second molecules other than CD40, CAP-1, TRAF-1 and TRAF-2.

As amended, claims 19 and 34 are directed to methods of identifying an effective agent that alters the association of CAP-1 with CD40 or a polypeptide that contains a TRAF domain. Applicants point out that new independent claims 38 and 42 are directed to methods of identifying an effective agent that alters the association of CAP-1 with CD40, and new independent claim 46

is directed to a method of identifying an effective agent that alters CAP-1 homodimerization.

Applicants submit that the specification provides adequate description for the full scope of the invention as now claimed and that one skilled in the art would recognize that Applicants were in possession of a genus of polypeptides containing TRAF domains capable of associating with CAP-1. In particular, Applicants submit that to show possession of a claimed genus, all that is required is to show that Applicant was in possession of the necessary common attributes or features of elements possessed by members of the genus. Applicants further note that adequacy of the description in the specification must be considered in view of what was known in the art at the time of filing and that description of the invention can be explicit, implicit, or inherent. In the present case, Applicants provide sufficient explicit description of a TRAF domain and exemplify several TRAF domain containing polypeptides that can be used in the claimed methods.

As set forth in the specification, TRAF domain containing polypeptides useful in the invention are characterized as having a conserved region known in the art as a TRAF domain, which is a region of about 150 amino acids residues representing position 385-536 of CAP-1, 254-406 of TRAF1 and 346-497 of TRAF2 (page 55, lines 18-23). Such TRAF domain containing polypeptides further are characterized as having an ability to associate with other TRAF domain containing polypeptides via their TRAF domains

(page 16, lines 5-16). In further describing this genus, the specification teaches several species of TRAF domain containing polypeptides useful in the invention, including CAP-1, TRAF1 and TRAF2 (page 54, lines 19-21). Thus, the specification discloses numerous exemplary species of TRAF domain polypeptides in addition to describing the common attributes of TRAF domain containing polypeptides useful in the invention.

In view of the above remarks, it is respectfully submitted claims 19 and 34 are supported by written description in the specification. Therefore, Applicants respectfully request that the rejection of claims 19 and 34 under 35 U.S.C. § 112, first paragraph, be removed.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, enablement

The objection to the specification and corresponding rejection of claims 19 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement in the specification, are respectfully traversed. Applicants respectfully submit that the specification provides enablement for the full scope of claims 19 and 34.

The enablement rejection set forth on pages 10-14 of the Office Action relates to the use for *in vivo* treatment of disease of an effective agent identified using a claimed method. Specifically, the basis for this rejection appears to be that "One cannot extrapolate the teaching of the specification to the

enablement of the claims because it appears that the use contemplated for the effective agent identified by the claimed method is the *in vivo* treatment of disease (page 10, last paragraph)."

Applicants respectfully point out that an effective agent obtained using a method of the invention need not be used for *in vivo* treatment of disease. In this regard, the specification teaches that an effective agent can be used to decrease the level of apoptosis and therefore can increase the survival time of a cell *in vitro*, for example, to improve yields in tissue culture applications (page 24, lines 5-11). Therefore, the enablement of the claims does not rely on the use of the effective agent for the *in vivo* treatment of disease.

Applicants point out that claims 19 and 34, as amended herein, are directed to methods of identifying an effective agent that alters the association of CAP-1 with CD40 or a polypeptide that contains a TRAF domain. Applicants submit that the specification provides those skilled in the art with guidance for making and using the claimed methods, for example, by teaching structural and functional characteristics of exemplary TRAF domain containing polypeptides; by teaching how to obtain and prepare a CAP-1; and by teaching how to determine that an agent alters association of CAP-1 with a second polypeptide.

Regarding structural characteristics of a polypeptide containing a TRAF domain, the specification teaches the structure of a TRAF domain, for example by delineating which amino acids of SEQ ID NO:2 correspond to the TRAF domain of a CAP-1 and referencing a source for the amino acid sequences of the TRAF domains of TRAF1 and TRAF2 (see, for example, Figure 3 and page 16, lines 7-10). Based on such structural characteristics, one skilled in the art would have identified TRAF domain containing polypeptides using routine methods such as sequence comparisons to detect a TRAF domain motif. Regarding functional characteristics of a polypeptide containing a TRAF domain, the specification teaches that a function of a TRAF domain containing protein is TRAF domain-mediated dimerization with another TRAF domain containing polypeptide (page 16, lines 7-16 and page 49, lines 20-22). The specification provides guidance to those skilled in the art for assessing TRAF domain dimerization by teaching methods for detecting protein-protein interactions, such as the two hybrid system (Example I) and the disclosed GST-fusion protein interaction method (Example II). Accordingly, using guidance provided in the specification for structural and functional characteristics of a TRAF domain containing polypeptide, only routine methods would have been needed for one skilled in the art to obtain a variety of TRAF domain containing polypeptides in addition to TRAF1, TRAF2 and CAP-1 for use in the claimed methods.

Furthermore, the specification provides those skilled in the art with guidance for preparing a CAP-1 for used in the claimed methods. In this regard, the specification provides the amino acid sequence of human CAP-1 as well as a corresponding encoding nucleotide sequence, and teaches that a CAP-1 can be obtained by routine methods, such as expressing a recombinant nucleic acid molecule encoding CAP-1 (page 14, lines 20-24). In addition, the specification teaches that a CAP-1 can be chemically synthesized (page 14, lines 24-28). In view of the guidance provided in the specification for preparing a CAP-1, Applicants submit that those skilled in the art would have been able to readily obtain a CAP-1 polypeptide for use in the claimed methods.

Moreover, the specification teaches a variety of assays for determining that an agent alters association of CAP-1 with a second polypeptide. The specification teaches, for example, that the yeast two hybrid assay (Example I); an *in vitro* interaction assay using GST-CAP-1 fusion proteins (Example II; see page 50, lines 26-33); as well as methods known in the art such as equilibrium dialysis (page 10, lines 26-29), can be used to detect association of CAP-1 with a polypeptide. In view of these teachings in the specification and knowledge in the art for detecting protein interactions, Applicants submit that those skilled in the art would have been able to detect altered association of a CAP-1 with a second polypeptide without undue experimentation.

The Office Action alleges that "one cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because although there is 57% and 59% identity between the TRAF domains of CAP-1 and TRAF1 and TRAF2, respectively, there is clearly a 43% as well as a 41%, respectively difference between CAP-1 and the two TRAFs." Applicants submit that the teaching in the specification of the % identity between CAP-1, TRAF1 and TRAF2 is sufficient for one skilled in the art to recognize that CAP-1 indeed contains a TRAF domain. Moreover, the teaching in the specification that TRAF domains in general are capable of homodimerization and heterodimerization would have led one skilled in the art to understand that the TRAF domain of CAP-1 can associate with TRAF domains of other polypeptides, with the TRAF domains of TRAF1 and TRAF2 being exemplary. Given that a TRAF domain motif would have been identified in a variety of amino acid sequences by one skilled in the art based on teachings in the specification as well as publication of the TRAF domain motif, only routine work would have been required to obtain a TRAF domain containing polypeptide and determine whether the polypeptide associates with CAP-1.

In view of the above, Applicants respectfully request removal of the rejection of claims 19 and 34 under 35 U.S.C. § 112, first paragraph.

Regarding the rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 19 and 34 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting the term "effective agent" is respectfully traversed. Applicants respectfully submit that the claims 19 and 34 are clear and definite as written.

The Office Action alleges that claims 19 and 34 are indefinite because they lack statement of the function to be achieved by the effective agent. Applicants respectfully disagree. As amended, claims 19 and 34 each recite in their preambles that an effective agent "alters the association of CAP-1 with a second polypeptide." Therefore, those skilled in the art would have understood that the function to be achieved by the effective agent is alteration of the association of CAP-1 with a second polypeptide. Therefore, Applicants respectfully request that this ground for rejection be removed.

Regarding the objection to claim 19

The Office Action states that claim 19 is objected to for allegedly missing a step. Claim 19 has been amended herein to correct a grammatical error and thereby indicate that CAP-1 is contacted with the second polypeptide and an agent suspected of being able to alter the association of the CAP-1 with the second polypeptide, wherein said second polypeptide is CD40 or a polypeptide containing a TRAF domain, under conditions suitable to allow association of CAP-1 with the polypeptide.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned agent with any questions related to this application.

Respectfully submitted,

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